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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,187	07/30/2003	Jurgen Engel	103832-477-NP	9817

7590 03/24/2006

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EXAMINER	
DELACROIX MUIRHE, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,187	ENGEL ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005 and 27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The following is responsive to the request for continued examination received Dec. 23, 2005 and the amendment received Oct. 27, 2005.

No claims are cancelled. No new claims are added. Claims 1-12 are currently pending.

All previous claim rejections set forth in the office actions mailed Nov. 3, 2004 and July 29, 2005 are withdrawn in view of applicant's amendment and the remarks contained therein.

Claim Objection(s)

1. Claims 6-7, 9 are objected to because of the following informalities: in claims 6 and 7, line 4, after "antitumor", the term –substance—should be added. Finally, in claim 9, line 4, the phrase "in a therapeutic dose which is effective for the treatment" should be cancelled. Appropriate correction is required.

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for breast carcinoma, does not reasonably provide enablement for treatment of all malignant and benign oncoses, i.e. cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement

requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to methods for treating benign and malignant oncoses, i.e. cancer, by administering an effective amount of a combination of a compound of Formula (I) or (II) and an antitumor agent.

(2) The state of the prior art

With respect to cancer, this a broad term which encompasses numerous forms of neoplastic diseases, each involving different types of tissues and organs and also includes blood borne diseases. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug or one drug combination, which is capable of treating all cancers in general. Please see pages 1226-1229 of Goodman & Gilman's.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular combination of drugs that is effective in treating all cancer types.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack of significant guidance from the present specification or prior art with regard to the treatment of all cancers in a mammal, including a human, with the claimed compounds as the active ingredients makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The claims are broad since they are drawn to the treatment of all cancer types.

(6) The amount of direction or guidance presented

The specification describes the use of combinations of the claimed compounds in the treatment of a limited number of cancers in a mammal, that is to say, breast carcinoma. However, Applicant's specification does not enable one of ordinary skill in the art to use the claimed invention in the treatment of the numerous neoplastic diseases covered by the term "benign or malignant oncoses"/cancer. Applicant's specification sets forth only one cancer cell type, which would be treated by the claimed combination(s). The specification does not provide guidance as to how one of ordinary skill in the art would accomplish the objective of treating all types of cancer in a patient by administering the claimed combination(s).

(7) The presence or absence of working examples

Example 1 investigates the effects of the administration of perifosine and cisplatin in vivo using rat mammary carcinoma model (pages 6-7). Example 2 (pages 7-8) investigates the effects of the administration of perifosine and cyclophosphamide in vivo using rat mammary carcinoma model. Finally, Example 3 investigates the effects of the administration of perifosine and adriamycin in vivo using rat mammary carcinoma model (pages 8-9).

(8) The quantity of experimentation necessary

It is acknowledged that Applicant is not required to enable each and every single embodiment encompassed by the claims, but must enable a sufficient number to be reasonably representative of that which is claimed. However, applicant has not enabled a sufficient number of cancer types that is reasonably representative of that which is claimed. In the absence of any sound evidence or scientific reasoning as to how the skilled artisan would extrapolate any results from breast cancer in the present disclosure as being reasonably suggestive of treating all forms cancer (in general), the present disclosure is not determined to be enabling for the treatment of all types of cancers.

Additionally, in light of the state of the art (see **(2)** above), which conspicuously lacks recognition that all forms of cancer are treatable by the administration of one drug or one combination of drugs, and in view of the unpredictability of effectively treating cancer, it is highly unlikely, and the Office would require experimental evidence to support the contention, that the claimed combination of compound(s) could actually treat all cancers by simply administering, by any method, an amount of the claimed compounds.

Given what is presently claimed, what is presently disclosed, and given what is supported by adequate description in the specification, one of ordinary skill in the art would have no alternative recourse ***but*** undue experimentation in order to determine how the present invention could be used to treat all forms of cancer malignant or benign.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 5, 7, 8, 10, 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "the approved antitumor [substance] is chosen from inhibitors of signal transduction in the form of high and low molecular weight inhibitors of receptor and/or cytosolic kinases" in lines 4-6. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the inhibitors" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitations "the drug product" and "the customary pharmaceutical carriers" in line 9. There is insufficient antecedent basis for this limitation in the claim.

In claims 5, 8, 10, the limitations "agonists or antagonists of natural hormones", "heterocyclic compounds" and "various cytostatics" render the claims vague and indefinite. These limitations are not defined by the claim, and the specification fails to provide any description for the "cytostatics", "heterocyclic compounds" and "agonist or antagonists of natural hormones" that are within the scope of the invention. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all of the criteria for patentability and whether the specification meets the criteria of 35

USC 112, first paragraph with respect to the claimed invention." Please see MPEP 2173.

Because the limitations "various cytostatics", "heterocyclic compounds" and "agonist or antagonists of natural hormones" would invite subjective interpretations of whether or not a particular cytostatic, heterocyclic compound or agonist or antagonist of natural hormones was included by or excluded from the present claims, the Examiner respectfully submits that the public would not be informed of the boundaries of what constitutes infringement of the present claims and thus the claims do not meet the requirements of 35 USC 112, second paragraph.

Additionally, in claim 7, the limitation "inhibitors of signal transduction in the form of high and low molecular weight inhibitors of receptor and/or cytosolic kinases" renders the claim vague and indefinite. The specification does not clearly set forth explicitly and with reasonable clarity the definition of "inhibitors of signal transduction in the form of high and low molecular weight inhibitors of receptor and/or cytosolic kinases" Instead, the description "these inhibitors may be selected from but not restricted to monoclonal antibodies and heterocyclic compounds" is merely exemplary and does not describe what would be excluded by the limitation. Please see page 4, [0011] of applicant's specification.

Again "the primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all of the criteria for patentability and whether the specification meets the criteria of 35 USC 112, first paragraph with respect to the claimed invention." Please see MPEP 2173.

Because the limitation would invite subjective interpretations of whether or not a

particular high and low molecular weight inhibitor of receptor and/or cytosolic kinases was included by or excluded from the present claims, the Examiner respectfully submits that the public would not be informed of the boundaries of what constitutes infringement of the present claims and thus the claims do not meet the requirements of 35 USC 112, second paragraph.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

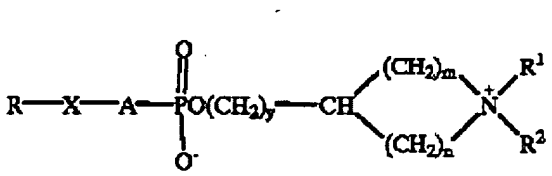
invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-12 rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al., 6,093,704 and Nickel et al., 6,696,428 and Nossner et al. 6,172,050 (all references already of record) in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition.

Nickel et al. '704 teach anti-tumor compounds such as miltefosine or octadecyl (1,1-dimethylpiperidinio-4-yl) phosphate, wherein said compounds are used in pharmaceutical compositions or dose units (i.e. drug products) for effective treatment of cancer. Please see col. 1, lines 10-17; col. 2, lines 40-44; claims 1-2.

Nickel et al. '428 teach anti-tumor compounds such as miltefosine or octadecyl (1,1-dimethylpiperidinio-4-yl) phosphate, wherein said compounds are used in pharmaceutical compositions or dose units (i.e. drug products) for effective treatment of cancer. Please see col. 1, lines 13-15; col. 2, lines 40-44; claims 1-2.

Nössner et al. disclose alkylphosphocholine compounds and their use in pharmaceutical compositions for treating tumors. The compounds are represented by the following General Formula (I):

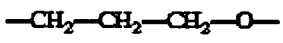


(I)

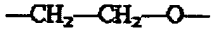
in which

R is a linear or branched alkyl radical having 10 to 24 carbon atoms, which can also contain one to three double or triple bonds, R^1 and R^2 independently of one another are hydrogen or in each case a linear, branched or cyclic saturated or unsaturated alkyl radical having 1 to 6 carbon atoms, which can also contain a Cl, OH or NH_2 group, it also being possible for two of these radicals to be bonded together to form a ring,

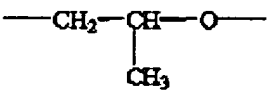
A is a single bond or one of the groups of the formulae



(II),

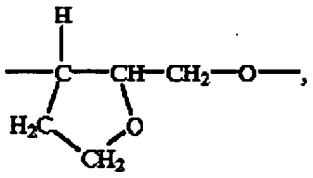


(III),



(V),

(VI)



the groups (II) to (VI) being orientated in such a way that the oxygen atom is bonded to the phosphorus atom of compound (I), X is an oxygen or sulphur atom or NH when A is a single bond, or an oxygen or sulphur atom when A is one of the groups (II) to (VI),

y is equal to 0 or a natural number between 1 and 3, and

m and n independently of one another are 0 or natural numbers, with the proviso that m+n=2 to 8.

Specific compounds claimed by applicant are found in the Examples as well as claims 5, 6. Nössner et al. disclose that these compounds have better anti-tumor activity than the open-chain derivatives. Please see col. 1-2; col. 2, lines 55-57; Examples 5, 18-21.

Nickel et al. '704 and '428 and Nossner et al. do not disclose a method of treating cancer or tumors by administering a combination of the disclosed alkylphosphocholine compounds and applicant's claimed antitumor agents. However, the examiner refers to Calabresi et al., which disclose in Table X-1 a list of known anti-tumor agents, such as 5-fluorouracil or cyclophosphamide etc., for treating cancers or tumors. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the methods of both Nickel et al. patents and the method of Nossner et al. by additionally administering the anti-tumor agents disclosed by Calabresi et al. because one of ordinary skill in the art would reasonably expect the combined properties of the anti-tumor compounds to effectively treat the patients suffering from tumors or cancer. Moreover, Calabresi et al. teach that drugs are generally more effective in combination and may be synergistic through biochemical

interactions. Please see page 1230, third full paragraph.

Conclusion

Claims 1-12 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
March 18, 2006

Cybille Delacroix-Muirheid
Patent Examiner Group 1600